EXHIBIT A116

American Journal of Epidemiology

Vol. 185, No. 1
DOI: 10.1093/aje/kww161
Advance Access publication: December 9, 2016

Systematic Reviews and Meta- and Pooled Analyses

Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies

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Initially submitted November 17, 2015; accepted for publication May 26, 2016.

Inflammation has been implicated in ovarian carcinogenesis. However, studies investigating the association between pelvic inflammatory disease (PID) and ovarian cancer risk are few and inconsistent. We investigated the association between PID and the risk of epithelial ovarian cancer according to tumor behavior and histotype. We pooled data from 13 case-control studies, conducted between 1989 and 2009, from the Ovarian Cancer Association Consortium (OCAC), including 9,162 women with ovarian cancers, 2,354 women with borderline tumors, and 14,736 control participants. Study-specific odds ratios were estimated and subsequently combined into a pooled odds ratio using a random-effects model. A history of PID was associated with an increased risk of borderline tumors (pooled odds ratio (pOR) = 1.32, 95% confidence interval (CI): 1.10, 1.58). Women with at least 2 episodes of PID had a 2-fold increased risk of borderline tumors (pOR = 2.14, 95% CI: 1.08, 4.24). No association was observed between PID and ovarian cancer risk overall (pOR = 0.99, 95% CI: 0.83, 1.19); however, a statistically nonsignificantly increased risk of low-grade serous tumors (pOR = 1.48, 95% CI: 0.92, 2.38) was noted. In conclusion, PID was associated with an increased risk of borderline ovarian tumors, particularly among women who had had multiple episodes of PID. Although our results indicated a histotype-specific association with PID, the association of PID with ovarian cancer risk is still somewhat uncertain and requires further investigation.

inflammation; neoplasms; histological type; ovarian neoplasms; pelvic inflammatory disease; risk factors

Abbreviations: AUS, Australian Ovarian Cancer Study/Australian Cancer Study (Ovarian Cancer); CI, confidence interval; CON, Connecticut Ovarian Cancer Study; DOV, Diseases of the Ovary and Their Evaluation; HAW, Hawaii Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; MAL, Danish Malignant Ovarian Tumor Study; NCO, North Carolina Ovarian Cancer Study; NJO, New Jersey Ovarian Cancer Study; NTH, Nijmegen Polygene Study and Nijmegen Biomedical Study; OCAC, Ovarian Cancer Association Consortium; OR, odds ratio; PID, pelvic inflammatory disease; pOR, pooled odds ratio; SON, Southern Ontario Ovarian Cancer Study; TOR, Familial Ovarian Tumor Study; UCI, University of California Irvine Ovarian Cancer Study; USC, Los Angeles County Case-Control Studies of Ovarian Cancer.

Ovarian cancer is the fifth most common cancer among women in developed countries, and it is the most fatal gynecological malignancy (1). The etiology of ovarian cancer is still not fully clarified, although a number of risk factors have been identified. A reduced risk of ovarian cancer has been observed with increased parity (2), use of oral contraceptives (2), hysterectomy (3), and tubal ligation (3), whereas family history of ovarian or breast cancer (2), use

of hormone replacement therapy (2), exposure to talc (4), and a history of endometriosis (5) have been associated with increased risks.

The 2 dominant hypotheses to explain the development of ovarian cancer relate increased risk to a large number of lifetime ovulatory cycles (the incessant ovulation theory) (6) or exposure to high levels of gonadotropins (the gonadotropin theory) (7). However, inflammation has also been suggested as a potential biological mechanism that may underlie a number of epidemiologic associations not easily explained by either theory (8, 9), including talc exposure, endometriosis, tubal ligation, and hysterectomy. Furthermore, a link between pelvic inflammatory disease (PID) and the risk of ovarian cancer has been suggested, and this potential association may also be explained by the inflammation theory. PID is defined as an upper genital-tract infection and includes diagnoses of endometritis, salpingitis, pelvic peritonitis, and tubo-ovarian abscess caused by microorganisms ascending from the lower genital tract (10). Approximately 800,000 women are treated for PID annually in the United States (11), and it is estimated that 6%–20% of all women in the Western world are diagnosed with PID during their lifetimes (12–14).

Epidemiologic studies investigating the association between PID and the risk of ovarian cancer and borderline ovarian tumors have been inconsistent, revealing increased risks in some studies (15–19) but not in all (20–23). Moreover, most previous studies have had methodological problems, including limited statistical power due to small numbers of study subjects and/or a short follow-up period. Also, ovarian cancer is a heterogeneous disease consisting of different histotypes with different risk factor profiles (24). However, few investigators have studied the role of PID separately for borderline tumors (15, 18) or for the separate histotypes of ovarian cancer (18, 20).

To examine the association of PID with the risk of ovarian cancer, an international collaborative study was performed, using data from 13 case-control studies participating in the Ovarian Cancer Association Consortium (OCAC). To our knowledge, this was the largest study of PID and ovarian cancer risk to date, thereby enabling a more robust estimation of risks among subgroups according to tumor behavior and histotype than has previously been possible.

METHODS

Participating studies

OCAC was founded in 2005 as an international forum of investigators conducting ovarian cancer case-control studies. The main aims of the collaboration are to discover associations between genetic polymorphisms and ovarian cancer risk and to identify and confirm epidemiologic risk factors for ovarian cancer (25).

For the present study, we obtained individual-level data from 13 case-control studies: 12 studies in OCAC (20, 26–37) and a parallel study not originally included in OCAC (Southern Ontario Ovarian Cancer Study (SON)) (38). Eight studies were conducted in the United States (Connecticut Ovary Study (CON), Diseases of the Ovary and Their Evaluation (DOV), Hawaii Ovarian Cancer Study (HAW), Hormones and Ovarian Cancer Prediction (HOP), North Carolina Ovarian Cancer Study (NCO), New Jersey Ovarian Cancer Study (NJO), University of California Irvine Ovarian Cancer Study (UCI), and Los Angeles County Case-Control Studies of Ovarian Cancer (USC)) (26, 27, 31–36), 2 in Canada (Familial Ovarian Tumor Study (TOR) and SON) (37, 38), 2 in Europe (Danish Malignant Ovarian Tumor Study (MAL) and Nijmegen Polygene Study and Nijmegen Biomedical Study (NTH)) (28–30), and 1 in Australia (Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer) (AUS)) (20).

Characteristics of the 13 included studies are presented in Table 1. Data were cleaned and checked for internal consistency, and clarifications were obtained from the initial investigators if needed. Women with nonepithelial ovarian tumors ($n = 186$) and with missing information on PID status ($n = 278$) were excluded, leaving 9,162 women with invasive ovarian cancer (hereafter denoted "ovarian cancer"), 2,354 women with borderline ovarian tumors, and 14,736 control participants for analysis. Eleven studies included both women with ovarian cancer and women with borderline ovarian tumors, whereas 2 studies included only women with ovarian cancer (NTH and NJO). Each study had approval from the relevant institutional review board or ethics committee, and all participants gave informed consent.

PID assessment

Information on PID was self-reported in all studies, through either in-person interviews ($n = 10$ studies) or self-administered questionnaires ($n = 3$ studies). Table 1 includes the phrasing of the question regarding PID status used in each study. We aimed to obtain information on the following PID variables: PID status (ever/never had PID), age at first PID episode, time since first PID episode, and number of PID episodes. All studies except for HAW had information on age at first PID episode, and 5 studies (CON, DOV, NJO, SON, and TOR) had data on number of PID episodes.

Statistical analysis

Associations between the PID variables and ovarian cancer risk were estimated using a 2-stage method (39). First, study-specific odds ratios were obtained from logistic regression models and were subsequently combined into a pooled odds ratio with 95% confidence intervals. The pooled estimate was computed by weighting each estimate by the inverse of the sum of its variance and the across-studies variance using a random-effects model (40). Only studies for which the study-specific model converged contributed to the pooled estimate. We used the Cochran Q and I^2 statistics to evaluate statistical heterogeneity between studies. If heterogeneity was present, we explored the potential sources of heterogeneity, including continent of study (North America vs. Europe vs. Australia) and method of data collection (in-person interview vs. self-administered questionnaire).

Table 1. Characteristics of 13 Ovarian Cancer Case-Control Studies From the Ovarian Cancer Association Consortium, Conducted in Australia, Europe, and North America Between 1989 and 2009

First Author, Year (Reference No.)	Study Name and Acronym	Study Period	Study Type	Method of Data Collection	Age Range, years	Matching Variable	Mean Interval From Ovarian Cancer to Interview, months	Response Rate, %		Wording of Question Concerning PID Status	No. and % of Controls Who Had Had PID		Missing PID Data
								Cases	Controls		No.	%	%
						Australia							
Merritt, 2008 (20)	Australian Ovarian Cancer Study/ Australian Cancer Study (Ovarian Cancer) (AUS)	2002–2005	Population-based	Self-administered questionnaire	18–80	Age (5-year categories)	5.3	84	47	Have you ever had pelvic inflammatory disease (e.g., chlamydia)? Have you ever had infection of the tubes or womb?	84	5.6	3.5
						Europe							
Glud, 2004 (28)	Danish Malignant Ovarian Tumor Study (MAL)	1995–1999	Population-based	In-person interview	31–81	Age (5-year categories)	3.6	81	68	Have you ever been told by a doctor that you had pelvic inflammatory disease, that is an infection in your uterus or tubes?[a]	416	26.6	0.7
van Altena, 2012 (29) Wetzels, 2007 (30)	Nijmegen Polygene Study and Nijmegen Biomedical Study (NTH)	1989–2008	Population-based	Self-administered questionnaire	23–83	No matching	85.3	63	42	Could you tell whether you have ever had inflammation of the tubes or ovaries?	13	2.2	0.0
						North America							
Risch, 2006 (34)	Connecticut Ovarian Cancer Study (CON)	1998–2003	Population-based	In-person interview	34–81	Age (3 age groups: 35–49 years, 50–64 years, and 65–79 years)	9.6	69	61	Could you tell me whether you have ever had an internal pelvic infection, sometimes called PID or pelvic inflammatory disease? We are not including bladder or vaginal infections in this.	23	4.2	0.2
Bodelon, 2012 (27)	Diseases of the Ovary and Their Evaluation (DOV)	2002–2009	Population-based	In-person interview	35–74	Age (5-year categories)	9.3	74	62	Before reference date, did a doctor or other health professional ever tell you that you had pelvic inflammatory disease or PID?[a]	65	3.5	0.3
Goodman, 2008 (31)	Hawaii Ovarian Cancer Study (HAW)	1993–2008	Population-based	In-person interview	18–93	Age (5-year categories), race/ ethnicity	10.9	78	80	Have you ever had PID or pelvic inflammatory disease? That is, have you ever had an infection in your tubes?	27	2.5	0.0

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Name and Acronym	Study Period	Study Type	Method of Data Collection	Age Range, years	Matching Variable	Mean Interval From Ovarian Cancer to Interview, months	Response Rate, %		Wording of Question Concerning PID Status	No. and % of Controls Who Had Had PID		Missing PID Data
								Cases	Controls		No.	%	%
Lo-Ciganic, 2012 (32)	Hormones and Ovarian Cancer Prediction (HOP)	2003–2009	Population-based	In-person interview	25–94	Age (5-year categories)	4.3	71	68	Before reference date, did a doctor or other health professional ever tell you that you had pelvic inflammatory disease (PID) or pelvic infection not related to surgery?[a]	22	1.2	0.0
Schildkraut, 2010 (35)	North Carolina Ovarian Cancer Study (NCO)	1999–2008	Population-based	In-person interview	20–75	Age (5-year categories), race/ ethnicity	6.2	67	60	Before you were diagnosed with ovarian cancer, had a doctor ever told you that you had pelvic inflammatory disease (or other pelvic infection)?[a]	37	3.4	0.3
Bandera, 2011 (26)	New Jersey Ovarian Cancer Study (NJO)	2002–2008	Population-based	In-person interview	23–88	No matching	11.4	47	40	Before reference date, were you ever told by a health professional that you had PID or pelvic inflammatory disease?[a]	2	0.4	0.9
Risch, 1994 (38)	Southern Ontario Ovarian Cancer Study (SON)	1989–1992	Population-based	In-person interview	25–80	Age (3 age groups: 35–49 years, 50–64 years, and 65–79 years)	4.8	71	65	Could you tell me whether you have ever had an internal pelvic infection? (PID or pelvic inflammatory disease—not including your bladder or vagina)	114	20.2	1.2
Zhang, 2011 (37)	Familial Ovarian Tumor Study (TOR)	1995–2003	Population-based[b]	In-person interview	21–94	Age (5-year categories)	21.4	50	80	Could you tell me whether you have ever had an internal pelvic infection, sometimes called PID or pelvic inflammatory disease? We are not including bladder or vaginal infections in this.	14	2.6	0.0
Ziogas, 2000 (36)	University of California Irvine Ovarian Cancer Study (UCI)	1993–2005	Population-based	Self-administered questionnaire	18–86	Age (5-year categories), race/ ethnicity	31.6	65	80	Have you ever been told by a physician that you have pelvic inflammatory disease?[a]	28	4.6	8.9

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Name and Acronym	Study Period	Study Type	Method of Data Collection	Age Range, years	Matching Variable	Mean Interval From Ovarian Cancer to Interview, months	Response Rate, %		Wording of Question Concerning PID Status	No. and % of Controls Who Had Had PID		Missing PID Data
								Cases	Controls		No.	%	%
Pike, 2004 (33)	Los Angeles County Case-Control Studies of Ovarian Cancer (USC)	1992–2009	Population-based	In-person interview	19–86	Age (5-year categories), race/ethnicity	8.1	73	73	Have you ever had PID or pelvic inflammatory disease? That is, have you ever had an infection in your tubes? Before [month/year], did a doctor ever tell you that you had PID or pelvic inflammatory disease?[b]	99	3.8	0.2

Abbreviation: PID, pelvic inflammatory disease.

[a] Studies classified as having a requirement that the diagnosis of PID be verified by a physician.

[b] Population-based cases and non–population-based controls.

For analyses, age at first PID episode and time since first PID episode were modeled both as categorical and continuous variables. Each categorical variable was categorized into ordinal groups (age at first PID episode: <20, 20–29, or ≥30 years; time since first PID episode: <10, 10–19, or ≥20 years; number of PID episodes: 1 or ≥2), with women who had never had PID as the referent. Associations between the continuous variables (age at first PID episode and time since first PID episode) and ovarian cancer risk were assessed only among women who had ever been diagnosed with PID. In order to model these associations, we included PID status in the model as a categorical indicator variable together with the continuous PID variable, as suggested by Leffondré et al. (41).

All analyses adjusted for age, parity (nulliparous vs. parous as well as parity as a continuous variable), oral contraceptive use (ever/never use as well as duration of use as a continuous variable), and family history of ovarian or breast cancer in a first-degree relative (yes/no) irrespective of their effect on the association between PID and ovarian cancer risk, because these factors were considered to be potentially important confounders a priori. For studies that used matching (age, race/ethnicity), conditional logistic regression analysis was used to adjust for these variables. In unmatched studies, age was categorized into 5-year age groups and unconditional logistic regression analysis was used (Table 1). When modeling parity and oral contraceptive use, the categorical variable was included as an indicator variable together with the continuous variable (41). Other potential confounders were considered but were not included in the final model, because none of them fulfilled an inclusion criterion of changing the log of the pooled estimate for ovarian cancer risk by 10% or more; these potential confounders were tubal ligation, hysterectomy, endometriosis, use of hormone replacement therapy, breastfeeding, age at menarche, menopausal status, body mass index, cigarette smoking, and educational level.

We examined interactions between PID status and parity (nulliparous vs. parous), oral contraceptive use (ever use vs. never use), and family history of ovarian or breast cancer in first-degree relatives (yes vs. no). Family history of breast or ovarian cancer was used as a proxy for hereditary ovarian cancer, as we aimed at exploring whether PID was similarly associated with hereditary and sporadic ovarian cancer. Linearity for all quantitative variables was examined by comparison with models with restricted cubic splines, but no appreciable deviations from linearity were found. The significances of the interactions and nonlinear associations were estimated by likelihood ratio tests of the interactions/nonlinearities and then comparison of the distribution of the study-specific P values with a uniform distribution by means of the Kolmogorov-Smirnov test (42).

All analyses were performed separately for ovarian cancer and for borderline tumors, and subgroup analyses were conducted by histotype. Ovarian cancers were divided into categories of serous, mucinous, endometrioid, clear cell, and other (including mixed cell, undifferentiated, and tumors of unknown epithelial histology). Additionally, serous cancers were divided into low-grade (grade 1) and high-grade

(grade 2 or higher) tumors, because these are considered to represent different histotypes (43). However, 2 studies had no information on grade (SON and TOR) and were therefore not included in these analyses; they were included only in the analyses for serous cancer overall. Subgroup analyses for borderline ovarian tumors included serous and mucinous tumors, because other histotypes of borderline ovarian tumors are rare. All *P* values were 2-sided, and the nominal level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using the statistical software R, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria), including the packages "survival," "meta," and "rms."

RESULTS

A history of PID was reported by 500 of the 9,162 women with ovarian cancers (5.5%), by 201 of the 2,354 women with borderline ovarian tumors (8.5%), and by 944 of the 14,736 control participants (6.4%). The proportion of control participants with PID varied across study sites, from 0.4% to 26.6%. In 11 of the studies, small proportions (less than 6%) of control participants reported PID, whereas in a Canadian study (SON) and in the Danish study (MAL), larger proportions of the control participants reported having had PID (20.2% and 26.6%, respectively). Median age at first PID episode was 28 years (interquartile range, 22–36 years) among women with ovarian cancer, 24 years (interquartile range, 20–30 years) among women with borderline ovarian tumors, and 25 years (interquartile range, 20–33 years) among control participants. Distributions of the various histotypes of ovarian tumors from the included studies are provided in Web Table 1 (available at http://aje.oxfordjournals.org/).

Ovarian cancer

In the pooled analysis, we found no association between a history of PID and the risk of ovarian cancer (odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.83, 1.19) (Web Table 2 and Figure 1). Furthermore, we observed no convincing associations of the age at first PID episode, time since first PID episode, or number of PID episodes with the risk of ovarian cancer (Web Table 2).

The magnitudes of the risk estimates for associations of specific histotypes of ovarian cancer with the individual

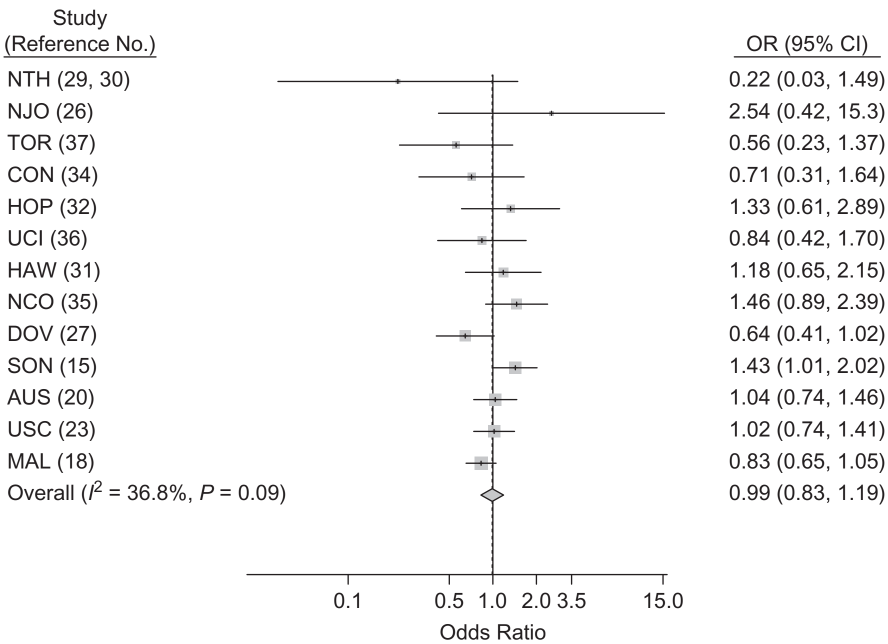

Figure 1. Associations between pelvic inflammatory disease (PID) status and the risk of ovarian cancer among the participants of 13 case-control studies in Australia, Europe, and North America, conducted between 1989 and 2009. Results are presented according to study site and overall and are adjusted for age, parity, oral contraceptive use (ever/never use and duration of use), and family history of ovarian or breast cancer (yes/no). For 4 of the studies (AUS, MAL, SON, and USC), results for the association between PID and ovarian cancer risk have been published previously (15, 18, 20, 23). For the remaining 9 studies, results for the association between PID and ovarian cancer risk have not been published previously, and their references therefore refer to papers with general information about these studies (26, 27, 29–32, 34–37). For the present study, we obtained individual-level data from all 13 studies directly from the Ovarian Cancer Association Consortium database. Each square and line represent the odds ratio (OR) and 95% confidence interval (CI), respectively, and the size of the square indicates the study weighting. AUS, Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); CON, Connecticut Ovarian Cancer Study; DOV, Diseases of the Ovary and Their Evaluation; HAW, Hawaii Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; MAL, Danish Malignant Ovarian Tumor Study; NCO, North Carolina Ovarian Cancer Study; NJO, New Jersey Ovarian Cancer Study; NTH, Nijmegen Polygene Study and Nijmegen Biomedical Study; SON, Southern Ontario Ovarian Cancer Study; TOR, Familial Ovarian Tumor Study; UCI, University of California Irvine Ovarian Cancer Study; USC, Los Angeles County Case-Control Studies of Ovarian Cancer.

PID variables did not differ from those observed for ovarian cancer overall, and only a few of the risk estimates reached statistical significance. However, we noted a higher risk of low-grade serous cancer (OR = 1.48, 95% CI: 0.92, 2.38) associated with PID status, although the risk estimate did not reach statistical significance (Web Table 2).

Borderline ovarian tumors

A history of PID was associated with a higher risk of borderline ovarian tumors (OR = 1.32, 95% CI: 1.10, 1.58) (Table 2 and Figure 2). Furthermore, women with 2 or more episodes of PID had a more than 2-fold higher risk of borderline ovarian tumors compared with women without a history of PID (OR = 2.14, 95% CI: 1.08, 4.24). We found no consistent trend in the risk of borderline tumors with age at first episode of PID (P-trend = 0.29) or time since first episode of PID (P-trend = 0.44).

As for borderline ovarian tumors overall, the risk of serous borderline ovarian tumors was statistically significantly increased among women with PID (OR = 1.43, 95% CI: 1.14, 1.79). Similarly, PID was also associated with an increased risk of mucinous borderline ovarian tumors, although the risk estimate was not statistically significant (OR = 1.28, 95% CI: 0.97, 1.68). The risks of serous and mucinous borderline ovarian tumors were not convincingly associated with age at or time since first PID episode. In addition, women with multiple episodes of PID had a higher risk of both serous and mucinous borderline ovarian tumors, but none of the risk estimates reached statistical significance (Table 2).

Additional analyses

To consider the possibility that early cancer symptoms might have been misinterpreted as PID or that an episode of PID might have resulted in further examinations that led to the identification of ovarian cancer, we performed sensitivity analyses of the association between PID status and the risk of ovarian cancer and borderline ovarian tumors by excluding women whose last PID episode was ≤1, ≤2, or ≤3 years before the date of diagnosis of ovarian cancer (for cases) or date of interview (for controls). The risk estimates in these sensitivity analyses were not substantially different from the risk estimates in the main analyses (data not shown).

We performed additional sensitivity analyses by stratifying studies by data collection method (in-person interview vs. self-administered questionnaire), study continent (North America vs. Europe vs. Australia), whether a physician-verified diagnosis of PID was required, study period (before or including 2000 vs. after 2000), proportion of control participants with PID (low (<6%) vs. high (>20%)), body mass index (calculated as weight (kg)/height (m)^2; <25 vs. ≥25), age at diagnosis of ovarian cancer (cases) or interview (controls) (<50 years vs. ≥50 years), and level of education (high school or less vs. more than high school). However, in the vast majority of these analyses, the direction and the magnitude of the associations were virtually unchanged compared with the associations obtained in the main analyses (data not shown). Notable exceptions were the observation of apparently statistically significantly increased risks of low-grade serous ovarian cancer (OR = 2.36, 95% CI: 1.24, 4.48) and endometrioid ovarian cancer (OR = 1.42, 95% CI: 1.01, 1.98) among women in the North American studies. However, no associations between PID and these 2 tumor types were found among the European studies or in the Australian study (low-grade serous cancer: pooled OR = 0.98, 95% CI: 0.61, 1.59 for the European studies and OR = 1.49, 95% CI: 0.52, 4.30 for the Australian study; endometrioid ovarian cancer: pooled OR = 0.60, 95% CI: 0.33, 1.10 for the European studies and OR = 1.09, 95% CI: 0.52, 2.26 for the Australian study).

Statistically significant heterogeneity across studies was observed for only a few of the risk estimates (Web Table 2 and Table 2). However, additional analyses showed that neither the method of data collection nor study continent nor proportion of control participants with PID could explain the observed heterogeneity since these additional analyses did not reveal increased consistency among studies of the same type (data not shown). We observed no effect modification between PID status and any of the potential risk factors (parity, oral contraceptive use, and family history of ovarian/breast cancer) for ovarian cancer and borderline ovarian tumors (all P values > 0.05) (data not shown).

DISCUSSION

To our knowledge, this was the largest study to date to have investigated the association between history of PID and the risk of ovarian cancer. In a pooled analysis of 13 case-control studies, we found no convincing associations between self-reported PID status and the risk of ovarian cancer overall, but suggestions of an increased risk of low-grade serous cancer were noted. For borderline ovarian tumors, an increased risk was observed among women with a history of PID, both overall and for serous and mucinous borderline tumors separately. Furthermore, the risk of borderline tumors increased with the number of PID episodes.

An association between PID and the risk of ovarian tumors is biologically plausible and could be explained by the inflammation hypothesis (8). Inflammation is characterized by the production of free radicals, cytokines, prostaglandins, and growth factors with the potential for genetic and epigenetic changes to the DNA, resulting in an increased risk of malignant transformation (44). Until recently, it was believed that all histotypes of ovarian cancer arose from the mesodermal surface epithelium, either on peritoneal surfaces or entrapped within the ovaries, and inflammation of the epithelium was therefore proposed to trigger malignant transformation (8). Recently, it has been suggested that some serous ovarian tumors originate in the mucosal epithelium of the fallopian tube, and inflammation of the fallopian tubes has been proposed to contribute to the development of these tumors (45).

The association between PID and the risk of ovarian cancer has been investigated in only 2 cohort studies (17, 19) and 7 case-control studies (15, 16, 18, 20–23). However, 4 of those case-control studies were based on data from study

Am J Epidemiol. 2017;185(1):8–20

Table 2. Adjusted Pooled Odds Ratios for the Association Between Pelvic Inflammatory Disease and Borderline Ovarian Tumors Among Participants in the Ovarian Cancer Association Consortium (Australia, Europe, and North America), 1989–2009

PID History	No. of Studies	No. of Controls	Overall			Serous Borderline Tumors			Mucinous Borderline Tumors		
			No. of Cases[a]	pOR[b]	95% CI	No. of Cases[a]	pOR[b]	95% CI	No. of Cases[a]	pOR[b]	95% CI
PID status	11										
Never had PID		12,755	2,153	1.00	Referent	1,184	1.00	Referent	891	1.00	Referent
Ever had PID		929	201	1.32	1.10, 1.58	114	1.43	1.14, 1.79	79	1.28	0.97, 1.68
Age at first PID episode, years	10										
Never had PID		11,679	1,976	1.00	Referent	1,101	1.00	Referent	804	1.00	Referent
<20		172	33	1.38	0.91, 2.09	16	1.28	0.73, 2.25	16	1.89	1.06, 3.35
20–29		355	87	1.52	1.17, 1.97	52	1.72	1.25, 2.38	32	1.60	0.94, 2.70
≥30		283	50	1.24	0.90, 1.73	27	1.38	0.89, 2.12	20	1.46	0.89, 2.40
P-trend					0.29			0.25			0.96
Per 1-year increment[c]				0.99	0.97, 1.01		0.98	0.96, 1.01		1.00	0.97, 1.03
Time since first PID episode, years	10										
Never had PID		11,679	1,976	1.00	Referent	1,101	1.00	Referent	804	1.00	Referent
<10		86	18	1.44	0.76, 2.73	12	1.74	0.86, 3.53	5	3.05	1.11, 8.40
10–19		159	48	1.73	1.21, 2.49	21	1.62	0.98, 2.70	25	2.37	1.46, 3.87
≥20		565	104	1.29	1.01, 1.64	62	1.48	1.09, 2.02	38	1.27	0.86, 1.86
P-trend					0.44			0.60			0.92
Per 5-year increment[c]				1.03	0.95, 1.12		1.03	0.89, 1.20		0.99	0.88, 1.12
No. of PID episodes	4										
0		3,287	662	1.00	Referent	349	1.00	Referent	282	1.00	Referent
1		142	25	0.88	0.55, 1.39	17	1.11	0.63, 1.95	8	0.84	0.33, 2.14
≥2		70	24	2.14	1.08, 4.24	12	3.28[d]	0.86, 12.54	11	1.98	0.80, 4.88

Abbreviations: CI, confidence interval; PID, pelvic inflammatory disease; pOR, pooled odds ratio.

[a] Numbers may not add up to totals due to missing values.

[b] Adjusted for parity (ever/never pregnant and number of pregnancies), oral contraceptive use (ever/never use and duration of use), and family history of ovarian or breast cancer (yes/no).

[c] Among women with a history of PID.

[d] *P* for heterogeneity < 0.05.

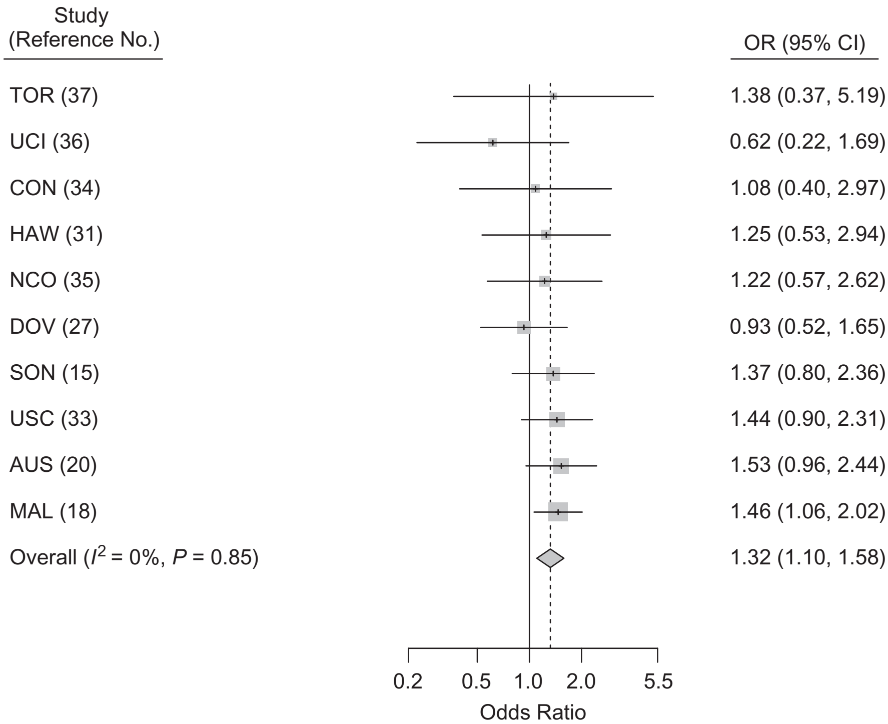

Figure 2. Associations between pelvic inflammatory disease (PID) status and the risk of borderline ovarian tumors among the pooled participants of 13 case-control studies in Australia, Europe, and North America, conducted between 1989 and 2009. Results are presented according to study site and overall and are adjusted for age, parity, oral contraceptive use (ever/never use and duration of use), and family history of ovarian or breast cancer (yes/no). For 2 of the studies (MAL and SON) results for the association between PID and the risk of borderline ovarian tumors have been published previously (15, 18). For the remaining studies, results for the association between PID and the risk of borderline ovarian tumors have not been published previously, and their references therefore refer to papers with general information about these studies (20, 27, 31, 33–37). For the present study, we obtained individual-level data from all studies directly through the Ovarian Cancer Association Consortium database. Each square and line represent the represent the odds ratio (OR) and 95% confidence interval (CI), respectively, and the size of the square indicates the study weighting. AUS, Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); CON, Connecticut Ovarian Cancer Study; DOV, Diseases of the Ovary and Their Evaluation; HAW, Hawaii Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; MAL, Danish Malignant Ovarian Tumor Study; NCO, North Carolina Ovarian Cancer Study; NJO, New Jersey Ovarian Cancer Study; NTH, Nijmegen Polygene Study and Nijmegen Biomedical Study; SON, Southern Ontario Ovarian Cancer Study; TOR, Familial Ovarian Tumor Study; UCI, University of California Irvine Ovarian Cancer Study; USC, Los Angeles County Case-Control Studies of Ovarian Cancer.

sites (MAL, USC, AUS, and SON) that were included in the present analysis (15, 18, 20, 23); results from those studies will not be discussed further. We found a 32% higher risk of borderline ovarian tumors associated with a history of PID, and risk estimates above unity were noted for nearly all individual studies. Furthermore, we observed similarly increased risks of serous and mucinous borderline tumors associated with PID status. Our novel finding of a 2-fold higher risk among women with multiple PID episodes may reflect a true association between PID and the risk of borderline ovarian tumors rather than being caused by chance or bias. Only 2 studies (SON and MAL, both included in the present analyses) have previously investigated the association between PID and the risk of borderline tumors (15, 18).

In the present study, the lack of any marked associations between PID and the risk of ovarian cancer overall is consistent with results from 1 case-control study (22), whereas 2 other studies found an increased risk of ovarian cancer (16, 17). Additionally, 2 studies assessed PID in relation to ovarian cancer risk but provided results only for ovarian cancer and borderline tumors combined, thereby hampering a comparison with the present results (19, 21); Ness et al. (21) reported null findings, and McAlpine et al. (19), in a Canadian cohort study, reported a 4-fold higher risk of ovarian cancer among women who had had PID. Concerning the histotypes of ovarian cancer, indications of an increased risk of low-grade serous cancer with PID were noted in the main analysis. Conversely, no convincing associations between PID and the risk of high-grade serous, mucinous, clear cell, or endometrioid ovarian cancer were noted in the main analyses. However, sensitivity analyses revealed statistically significantly increased risks of low-grade serous and endometrioid ovarian cancers when using data from the North American studies only. Other than 2 studies already included in the present pooled

analysis, no previous studies have assessed the association between PID and the risk of ovarian cancer according to histotype. Although we cannot completely rule out the possibility that these histotype-specific findings may be due to chance, the present study is the first, to our knowledge, to indicate differences in the risk profile of ovarian cancer histotypes with regard to PID. However, the low number of exposed cases for most of the histotypes limited the precision of the risk estimates, and our results must therefore be confirmed by others.

Nevertheless, our results suggest that PID may be differentially associated with the risk of ovarian tumors. Reasons for this difference are not known, but they may be associated with different pathogeneses of the ovarian tumor histotypes. Recently, the so-called dualistic model of ovarian carcinogenesis proposed that borderline tumors are precursors of type 1 (low-grade) ovarian cancers but unrelated to type 2 (high-grade) ovarian cancers (46). According to this hypothesis, type 1 tumors include low-grade serous and mucinous carcinomas, and these are believed to develop along a continuum of tumor progression from adenoma to borderline tumor to invasive carcinoma (46). Clear cell and low-grade endometrioid carcinomas are also type 1 cancers and are believed to develop from endometriosis. Our results demonstrated an association between PID and the risk of borderline ovarian tumors and indicated that the risk of low-grade serous cancer might also be increased, which accords well with the theory of a stepwise development from a serous borderline tumor to low-grade serous cancer. In contrast, no associations between PID and high-grade serous ovarian cancer were observed. Therefore, our results suggest that PID is a risk factor for borderline and possibly also low-grade serous ovarian cancer, whereas no marked associations were observed for the other histotypes of ovarian cancer. The possible underlying biological mechanisms responsible for this differential association between PID and ovarian tumor types are unknown and require further investigation in epidemiologic and biological studies.

A strength of the present study is the use of pooled data from 13 case-control studies. The large sample size resulted in increased statistical power and enabled us to estimate risks according to invasiveness and histotype. Moreover, all the studies we included were population-based, and information on PID was obtained through in-person interviews in the majority of them. In addition, we used individual-level data carefully harmonized and entered into a single data set. The use of a 2-stage approach (39) enabled us to account for differences in design and data collection between studies and to control for several potential confounders. Finally, all studies with the relevant exposure data in OCAC were included regardless of their individual results, thus removing the influence of publication bias.

Some limitations should also be mentioned. First, information about PID status was self-reported in all studies, and the proportion of control participants reporting an episode of PID in the individual studies ranged from 0.4% to 27%. Unfortunately, most studies had no data or insufficient data on treatment for PID, which could have added important information in terms of validating the PID diagnoses. The highest frequencies were reported in the Danish study (MAL: 27%) and in a Canadian study (SON: 20%); the remaining 11 studies all had PID proportions below 6%. Reasons for the differences in proportions among the studies may include geographic variation in the prevalence of PID-causing pathogens, different phrasing of the PID-related questions, or differences in the prevalence of high-risk sexual behaviors. However, we believe that underestimation of PID exposure is the most likely cause for the low proportions of women with a history of PID in the majority of studies, because previous studies from Sweden and the United States have estimated lifetime prevalences of PID between 6% and 20% (12–14). In studies with self-reported data on PID exposure, including the present study, the true proportion of women who have had PID might be underestimated for several reasons—women might have forgotten about a past PID episode, chosen not to report it, or had unrecognized, subclinical PID. Hence, we cannot rule out the possibility that this misclassification of PID status could have influenced our results. Interestingly, investigators in only 2 previous studies did not use self-reported data on PID but instead obtained information on PID from a population-based health insurance database or used evidence of inflammation at surgery for tubal damage as a proxy for previous PID, and both groups reported an increased risk of ovarian cancer associated with PID (17, 19). Therefore, in future studies, researchers should consider using a more objective measure of PID, such as data obtained from reliable health registries or through serological testing for antibodies to PID-causing pathogens, including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Second, misclassification of PID exposure might also result when women mistakenly report bladder or vaginal infections as PID. However, we expect this misclassification to be relatively infrequent, because in the majority of included studies, PID was defined as diagnosed by a physician, or the question specified that bladder or vaginal infections were not included. Furthermore, the majority of studies performed in-person interviews, thus allowing for potential uncertainties to be clarified. Third, the retrospective design of case-control studies introduces the potential for recall bias, in which case patients are more likely than control participants to report past exposures. However, we would not expect such overreporting to be differential with respect to degree of invasiveness of diagnosed ovarian tumors, and we therefore do not believe that this can explain the increased risk we observed for borderline tumors but not for ovarian cancer. Fourth, surveillance bias is potentially of concern, because women with PID symptoms may undergo ultrasonography or laparoscopy during which the ovaries are visualized, leading to coincidental findings of ovarian tumors. However, this potential surveillance bias is probably minimal, because our sensitivity analyses excluding women with PID less than 1–3 years in the past revealed virtually identical results as in the main analyses. Fifth, only 5 studies had information on the number of PID episodes, and the absence of thorough information on this exposure variable limited our ability to fully investigate and interpret any potential dose-response associations between number of PID episodes and the risk of ovarian cancer and borderline ovarian tumors. Finally, despite the

large study size, we still had limited statistical power because of small proportions of women with PID in some of the categorical analyses and for some of the rarer histotypes, and we cannot completely rule out the possibility that some of the observed associations may have been be due to the large number of comparisons; thus our results should be interpreted with caution.

In conclusion, in this large, pooled analysis, we observed an increased risk of borderline ovarian tumors among women with a history of PID. These risks increased with the number of PID episodes. Conversely, we found no association between PID and the risk of ovarian cancer overall, but indications of an increased risk of low-grade serous cancer were noted. These findings suggest that PID may be a risk factor for borderline ovarian tumors and possibly for low-grade serous cancer, although no convincing associations were seen for other ovarian cancer histotypes. However, until the specificity of the association is confirmed in additional epidemiologic and biological studies, the association between PID and ovarian cancer risk is still somewhat uncertain.

ACKNOWLEDGMENTS

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This work was supported by the European Commission's Seventh Framework Programme grant 223175 (HEALTH-F2-2009-223175). It was also supported by the US National Institutes of Health (grants R01 CA074850 and R01 CA080742 (CON); R01 CA112523 and R01 CA87538 (DOV); R01 CA58598, N01 CN55424, and N01 PC 67001 (HAW); R01 CA95023, K07 CA080668, and P50 CA159981 (HOP); R01 CA61107 (MAL); R01 CA76016 (NCO); P30 CA072720, K07 CA095666, R01 CA83918, and K22 CA138563 (NJO); R01 CA063678, R01 CA149429, and R01 CA063682 (TOR); R01 CA058860, R01 CA092044, and PSA 042205 (UCI); P01 CA17054, P30 CA14089, R01 CA61132, N01 PC67010, R03 CA113148, R03

CA115195, and N01 CN025403 (USC)); Danish Cancer Society (grant 94 222 52 (MAL)); Mermaid 1 (MAL); US Army Medical Research and Materiel Command (grant DAMD17-01-1-0729) (AUS); National Health and Medical Research Council of Australia (grants 199600 and 400281 (AUS)); Cancer Councils of New South Wales, Victoria, Queensland, South Australia, and Tasmania (AUS); Cancer Foundation of Western Australia (AUS); US Department of Defense (grants DAMD17-02-1-0669 (HOP) and DAMD17-02-1-0666 (NCO)); Cancer Institute of New Jersey (NJO); Radboud University Nijmegen Medical Centre (NTH); Lon V Smith Foundation (grant LVS-39420 (UCI)); and California Cancer Research Program (grants 00-01389V-20170 and 2II0200 (USC)). The Ovarian Cancer Association Consortium is supported by a grant from the Ovarian Cancer Research Fund.

Penelope Webb and Susan Jordan wrote on behalf of the Australian Ovarian Cancer Study Group. The Australian group thanks all the clinical and scientific collaborators for their contribution (AUS). The cooperation of the 32 Connecticut hospitals, including Stamford Hospital, in allowing patient access is gratefully acknowledged (CON). The MAL study is grateful to Nick Martinussen for data management assistance. We are grateful to the family and friends of Kathryn Sladek Smith for their generous support of the Ovarian Cancer Association Consortium through their donations to the Ovarian Cancer Research Fund.

Certain data from the Connecticut Ovarian Cancer Study were obtained from the Connecticut Tumor Registry, Connecticut Department of Public Health. The Connecticut Ovarian Cancer Study investigators assume full responsibility for analyses and interpretation of these data.

Conflict of interest: none declared.

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